

Penetration of tobramycin sulphate into the human eye

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SUMMARY Tobramycin sulphate, a new aminoglycoside antibiotic, was injected intramuscularly (80 and 100 mg) and subconjunctivally (10 mg) into patients, and the concentrations of the drug in serum and aqueous humour were determined 1 hour after the injection by an agar wall diffusion plate method. The intramuscular administration of tobramycin produced insignificant and non-inhibitory concentrations in the aqueous humour, while therapeutically effective levels of the antibiotic appeared in the aqueous after subconjunctival administration of tobramycin (mean: 18.9 µg/ml). These data suggest that tobramycin sulphate may be of value in the treatment of ocular infections.

Aminoglycosides are broad spectrum antibiotics widely used in the treatment of ocular infections and for postoperative prophylaxis. Tobramycin sulphate is a new water-soluble, parenterally administered antibiotic of the aminoglycoside group, derived from *Streptomyces tenebarius*. Its chemical structure, kinetics, pharmacodynamics, and antimicrobial properties closely resemble those of gentamicin (Bodey and Stewart, 1972; Dienstag and New, 1972). It has been proved that tobramycin is more effective than gentamicin against pseudomonas strains *in vitro* (Traub and Raymont, 1972; Levison and Kaye, 1974; Wretling and Gezelius, 1976), and it has been reported that it seems to be less toxic than gentamicin (Federspil, 1974). The peak serum concentration of tobramycin occurs between 30 and 90 minutes after intramuscular administration, and detectable levels persist for as long as 6 to 8 hours (Goodman and Gilman, 1975). There is some information on the intraocular penetration of tobramycin in rabbits (Purnell and MacPherson, 1974; Uwayadah and Faris, 1976), but the penetration of the antibiotic into the human eye after administration by various routes has not yet been reported.

The present study was carried out to determine the concentration of tobramycin sulphate in the serum and aqueous humour of patients after intramuscular and subconjunctival administration of the antibiotic.

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Patients and methods

Thirty-one patients, aged 58 to 82 years, scheduled for routine cataract extraction under local anaesthesia were selected for this study. All had a normal anterior segment on clinical examination and none of them had a history of drug allergy, renal disease, or any other contraindications to tobramycin administration.

The patients were divided into 3 groups as follows: In the first group each one of 9 patients was given 80 mg of tobramycin in a single intramuscular injection; in the second group each of 7 patients was given 100 mg in a single intramuscular dose; in the third group each of 15 patients was given 10 mg of tobramycin subconjunctivally in the eye to be operated upon. The eye was anaesthetised with benoxinate 0.4% eye drops, and 0.25 ml (10 mg) of the tobramycin solution was injected subconjunctivally in the inferior half of the globe by means of a tuberculin syringe with a 27 G needle. The patients in all 3 groups received the antibiotic 1 hour before operation. The eyes were prepared for routine cataract extraction. On the operating table, after retrobulbar anaesthesia, lid block, and conjunctival flap dissection, a keratome making a 3 mm incision was inserted in the anterior chamber at 12 o'clock. Simultaneously a tuberculin syringe with a 25 G needle was introduced into the chamber below the keratome and 0.2 ml of aqueous humour was aspirated. At the same time a venous sample (4 to 5 ml) was also collected. The operation was continued in routine fashion. The blood and

Table 1 Human serum and aqueous humour tobramycin levels in $\mu\text{g/ml}$ 60 minutes after a single intramuscular injection (80 mg in group I and 100 mg in group II) and a single subconjunctival injection of 10 mg of tobramycin (group III)

Subjects	Group I		Group II		Group III	
	Serum	Aqueous	Serum	Aqueous	Serum	Aqueous
1	2.0	0.7	3.1	0.4	1.15	17
2	2.8	0.2	5.2	1.6	1.10	20
3	5.0	0.2	4.2	1.3	1.15	15
4	1.5	0.3	11.0	1.9	0.57	16
5	2.8	0.8	6.0	0.2	0.40	20
6	9.0	0.2	11.0	2.6	0.36	18
7	5.0	0.3	8.4	1.4	0.38	22
8	5.2	0.2			0.78	17
9	3.3	0.2			1.40	19
10					0.80	23
11					0.50	12
12					1.12	21
13					0.90	20
14					0.42	24
15					0.20	20
Mean	4.07 \pm 2.28	0.30 \pm 0.26	6.9 \pm 3.21	1.34 \pm 0.8	0.74 \pm 0.37	18.9 \pm 3.17

aqueous samples, packed in ice, were delivered within 1 hour to the laboratory for antibiotic assay.

ASSAY METHOD

The antibiotic concentration in serum and aqueous humour was determined by an agar wall diffusion plate method (Bennett *et al.*, 1966). Petri dishes contained a base agar layer (pH 6.8), overlaid with a seeded layer prepared with a suspension of *Bacillus subtilis* NCTC 8236 as test organism. Small holes (4.5×2.5 mm) were opened and filled with samples. All samples were run in duplicate. Using standard concentrations of six different tobramycin solutions a standard curve was plotted on semilog paper. The diameter zones were measured in millimetres by a microestimator after 24 hours of incubation at 37°C . Concentrations of the antibiotic were determined in $\mu\text{g/ml}$ by reading the concentration directly from the standard curve derived simultaneously from the similarly prepared known concentration of antibiotic diluted in human serum and saline.

Results

The concentrations of tobramycin sulphate found in the aqueous humour and serum 1 hour after intramuscular and subconjunctival antibiotic ad-

ministration are listed in Table 1 and are shown in Fig. 1 schematically.

Group I. A single intramuscular injection of 80 mg of tobramycin resulted in a mean serum level of $4.072 \pm 2.28 \mu\text{g/ml}$ and a mean aqueous concentration of $0.3 \pm 0.26 \mu\text{g/ml}$.

Group II. 100 mg of tobramycin injected intramuscularly produced a mean serum concentration of $6.94 \pm 3.2 \mu\text{g/ml}$ and an average aqueous humour level of $1.33 \pm 0.8 \mu\text{g/ml}$.

Group III. Sixty minutes after a single subconjunctival dose of 10 mg (0.25 ml) of tobramycin sulphate the mean antibiotic serum level was $0.74 \pm 0.37 \mu\text{g/ml}$ and the average tobramycin aqueous concentration was $18.9 \pm 3.17 \mu\text{g/ml}$.

All the patients had a normal postoperative course and none showed any anterior segment changes resulting from the subconjunctival injection of tobramycin.

Discussion

The treatment of ocular infections caused by Gram-negative bacteria, and especially by *Pseudomonas aeruginosa* strains, cannot be regarded as satis-

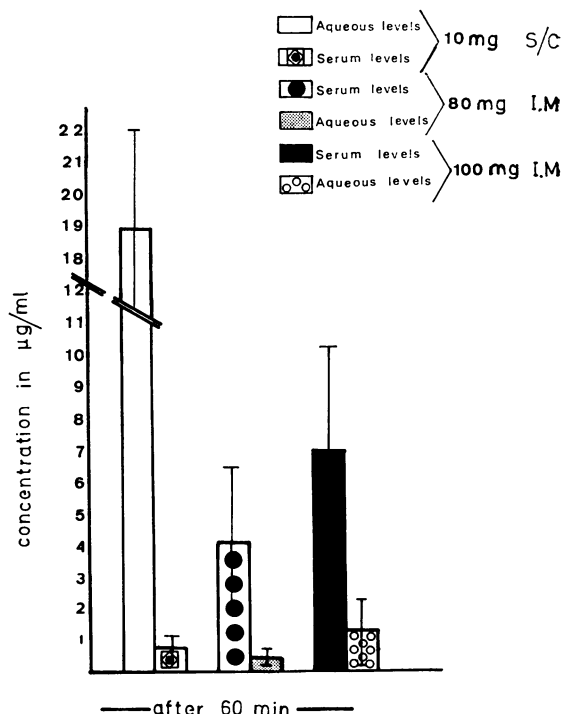


Fig. 1 Mean serum and aqueous humour tobramycin levels following intramuscular and subconjunctival injection in man

factory. Tobramycin sulphate is a new antibiotic of the aminoglycoside group that seems to be more effective, at least *in vitro*, against these bacteria, as reported previously. Our results show that tobramycin penetrates the eye poorly after intramuscular injection, while therapeutically effective concentrations in the aqueous humour resulted from subconjunctival administration.

The intramuscular injection of tobramycin in a single dose of 80 mg produced aqueous levels of the antibiotic ($0.3 \pm 0.26 \mu\text{g/ml}$) which are much lower than the minimum inhibitory concentration for the majority of the pathogenic bacteria (Jaffe *et al.*, 1974). When 100 mg of tobramycin was injected intramuscularly, the antibiotic level produced in the aqueous fluid ($1.33 \pm 0.8 \mu\text{g/ml}$) was 4 times higher than that produced by the intramuscular injection of 80 mg. This antibiotic level in the aqueous can be effective against some bacteria, but undesirable side effects may be produced by a dose of 100 mg of tobramycin. The inability of tobramycin to penetrate the normal human eye in therapeutic levels was expected and is consistent with published data on other aminoglycosides to which tobramycin is related (Litwak *et al.*, 1969; Furgiele, 1970; MacIwain *et al.*, 1974). When 10 mg of tobramycin was injected subconjunctivally, the antibiotic level produced 1 hour after administration was much higher than the minimum inhibitory concentration of all the pathogenic bacteria, even *Pseudomonas* species (Jaffe *et al.*, 1974). The levels of antibiotic obtained in the aqueous after subconjunctival injection are higher than those of other antibiotics of the same group (Furgiele, 1970; MacIwain *et al.*, 1974). The variations in the mean values of tobramycin aqueous levels observed in our experiments are consistent with other data on tobramycin and other aminoglycosides (Litwak *et al.*, 1969; Uwaydah and Faris, 1976).

Finally, we can conclude that tobramycin levels in the aqueous humour obtained from subconjunctival administration were sufficient to inhibit all strains of pathogenic bacteria, while an efficient barrier prevents the diffusion of tobramycin from serum to the primary aqueous humour of the normal human

eye. The intramuscular administration of the antibiotic produces subtherapeutic levels in the aqueous humour.

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